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COGNITIVE AGING, BIOLOGICAL LIFE EVENTS AND PRIMITIVE REFLEXES

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SUMMARY

Many cognitive abilities decrease with increasing age. Especially memory executive functions and slowness are relevant in this respect. Up till now this has been regarded as a reflection of the 'normal' physiological aging process. However, this paper shows that age-extrinsic factors determine cognitive performance more then calender age per se. Healthy subjects with so called Biological Life Events (BLE) appear to be characterized by inferior performance on various cognitive tests. In addition, primitive reflexes are especially present in subjects with BLE or in non-demented patients with memory dysfunctions. The findings suggest that it is important to take health-related factors such as the BLE in consideration in cognitive gerontological research. They may have a causal role in altering brain function and thus give rise to altered brain processes such as manifested by cognitive changes.

Key words: Aging - Risk factors - Memory - Cognitive function - Primitive reflexes.

INTRODUCTION

It has been established that many cognitive abilities -generally- decrease with increasing age. Especially memory functions, attentional functions, and various motor functions deteriorate. Also, planning of new activities, problem solving and complex decision making (the executive functions) as well as flexibility are noticeable diminished. In addition, there appears to be a general slowness, especially in the performance of task which have to be carried out under time pressure and/or in demanding situations (for review, see 1, 2). A general slowing down of central nervous system activity is thought to underly this mental slowness.

There is an increasing number of middle-aged and -especially- elderly people who complain about cognitive impairments and who are afraid that the dysfunctions are a manifestation of an incipient dementia. However, uncertainty exists whether cognitive decline is an essential feature of the aging process. There are some publications which show that variability of performance in cognitive tests increases with age (references in 3). In addition, various findings show that not all individuals decline at the same rate (4) and that environmental factors related to education (5) or to hobbies and activities (5,6) have an influence on cognitive performance in older individuals apart from the factor 'age'.

With respect to biological factors, the issue is less clear. It has been tacitly assumed in gerontological research, that individuals who are not diseased can therefore be regarded as normal and healthy; there are some publications who suggest that health-related factors do not play a major role in cognitive performance at higher age (6). However, other findings give strength to the notion that biological conditions such as health related factors are important in determining the extent to which cognitive deterioration with age takes place. Rowe and Kahn (7), for example, advocate a distinction between 'usual aging' and 'succesful aging', the latter meaning that there are no functional changes other than those which are age-intrinsic. Usual aging is a term which denotes the condition in which age-extrinsic factors are added to the age-intrinsic processes. Usual aging would thus be determined by biological factors which are not regarded as pathological. A question remains as to the nature of these age-extrinsic factors.

The present paper reviews recent evidence which suggest that socalled Biological Life Events (BLE; 8, 9) can be regarded as important age-extrinsic factors which are more important for cognitive functioning than calender age per se. First, evidence will be given which is derived from a large cross-sectional study into cognitive aging in which healthy subjects aged 20 through 80 with and without BLE were compared. Second, experiments are described in which socalled

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'primitive reflexes' (PR) were investigated in otherwise healthy subjects. When primitive reflexes are found in adult subjects, they are -generally- regarded as a subtle measure of structural changes in the brain (10). The evidence is reviewed that the prevalence of PR is higher in elderly subjects with cognitive dysfunctions. In the concluding remarks, suggestions to the impact of these findings are made. Discussions as to the influence of BLE on cognitive functioning are given elsewhere (11, 12, 13).

COGNITIVE FUNCTION AND BIOLOGICAL LIFE EVENTS

Cognitive dysfunctions in relation to well established disease states such as moderate to severe trauma, depression and chronic alcoholism are well established. However, the issue is, whether conditions with unknown or ambiguous relation to brain and cognitive (dys)function -such as very mild head injury, social drinking, increased blood pressure, anaesthesia or diabetes mellitus- have some influence on cognitive functioning.

Recently, the term 'Biological Life Events' (BLE) was proposed by Houx and Jolles (8,9) to define "those factors which are related to physical and mental health, experienced at any part in life and thought to be related to brain dysfunctioning, other than grossly impairing conditions like dementia and brain trauma". Relevant BLE are the following (see 9, 11, 12 for operational definition): 1) (Very) mild head injury, 2) surgery under general anaesthesia, 3) mild to moderate use of alcohol, 4) use of medication which affects driving ability or consciousness, 5) exposure to neurotoxic factors, 6) early childhood or developmental problems, or minor diseases in the realm of 7) neurology, 8) psychiatry, or 9) internal medicine which have never been related to cognitive functioning (e.g. migraine, slight renal dysfunction a slight diabetes mellitus). Interestingly, several recent studies are in favour of the notion that these health-related conditions have an influence on cognitive functioning. For instance, Elias and coworkers (15) found main effects of hypertension on neuropsychological functions. Hartman in his extensive review (16) reports on the neuropsychological side effects of medication, and of various anaesthetics, and on the effects of mild to moderate alcohol consumption.With respect to the effects of mild brain trauma there is an increasing number of studies which suggest that persisting cognitive aftereffects may occur in up to 35% of subjects (e.g. 17). Finally, growing evidence points to the influence of systemic diseases on cognitive functioning.

Houx, Vreeling and Jolles (8, 11, 12) devised a large cross-sectional study in subjects who were regarded as normal and healthy according to all criteria used in gerontological research. Two hundred and forty-seven subjects were selected from a larger group of volunteers who regarded themselves as healthy. Out of this larger group, more than 200 subjects were excluded on the basis of interview or medical examination. These subjects were healthy according to self-report but appeared to suffer from major brain damage by trauma, stroke or a major disease in the realm of neurology, psychiatry or internal medicine. The resulting group of 247 subjects had no apriori likelihood of brain dysfunction or cognitive dysfunctions attributable to a major neurological or psychiatric illness. This group was now screened for BLE (for scoring and cut-off values see 8, 11, 12). Subjects who were characterized by one or more BLE were assigned to one of seven BLE groups with mean ages ranging from 20 to 80 years (20, 30, 40, 50, 60, 70, and 80 years). Subjects without BLE were assigned to a corresponding optimally healthy age group. The subjects were then subjected to a battery of neurocognitive tests. These included primary memory span; memory scanning (MST); visual verbal learning; Stroop Colour-Word test; concept shifting (CST); finger tapping; a multiple choice reaction test (MCRT).

The results showed that there is clearly a differential effect in that particular test performances are more vulnerable to age and BLE than others. Primary memory span was least clearly related to age but a marked effect of BLE was found, especially at higher age. In addition, there was a decrease in information processing which may help explain why elderly and even middle-aged people who do not experience significant perceptual or intellectual deficits often do have difficulties with processing all information presented to them. These problems may well originate from a general reduction in the speed of information processing, already there in the fourth decade, but manifest especially after the sixth or seventh decade. In spite of the fact that the total amount of reproduced words in the word learningtest was somewhat reduced with advancing age, there was a remarkable exception to the rule that age affects memory. Maximum recall and recognition of memorized words was not affected at all in the group of subjects who had not experienced BLE, showing that decline of certain aspects of memory functioning is related to other factors than mere calender age. BLE accounted for a large -if not the largest- part of the inter-individual differences. Delayed recall in elderly BLE-affected subjects was very poor.

Effects on language interference were found (Stroop test) and also, the interference effect of concept shifting increased with age. The MCRT showed that Simple reaction time was not affected very much in healthy elderly subjects. However, responses that are incompatible to the stimulus demand considerably longer latencies. This latency in BLE-affected elderly individuals dramatically increased in BLE-affected subjects, with reaction times of over one second.

In summary, significant age-associated decline was observed in all aspects of cognitive functioning that were studied. Of the four main areas of cognition that were identified, memory showed the least decline, and cognitive speed the greatest. The same was true regarding the age-related increase in variability of test performance. Taking Biological Life Events (BLE) into account much attenuated this decline, however. Subdivision of the total sample of subjects -all regarding themselves normal and healthy- into BLE-free and BLE-affected showed large group differences. Compared to the over-all averaged performance, age differences were much smaller when BLE were absent, and greatly enhanced when they were present. These findings argue strongly in favour of the notion (see above) that BLE are age-extrinsic factors which have a stronger impact on cognitive functioning then calender age per se.

Another series of experiments was performed by Bohnen and Jolles in order to find whether other age-extrinsic factors might also be of relevance. Nutritional factors were assessed in relation to cognition because of a growing number of papers which suggests that vitamins and particular bivalent metals may have an important influence on the brain. In a cross-sectional aging study (19, 20) four age groups (20, 40, 60, and 80 years of age) were compared. Twenty very healthy BLE-free subjects were assigned to each age group. They were tested on cognitive tasks and various blood parameters were taken, including metals and vitamins. It was found that subjects high and low in blood levels of zinc were different in their performance on a complex speed task (19). Similar results were found with respect to vitamin B12 (20). These results suggest that nutritional factors may indeed have impact on cognitive aging; in addition, nutritional factors can tentatively be considered another age-extrinsic factor with influence on cognitive functioning additional to the influence of calender age per se.

COGNITIVE FUNCTION AND PRIMITIVE REFLEXES

Given the findings described above, it is an interesting question whether the inferior cognitive performance which appears to be characteristic for subjects with BLE is consequence of changes in brain functioning. BLE, by definition, are conditions with a putative influence on the brain. It was therefore deemed important to investigate whether other indicators would exist of changes in brain function in subjects with BLE as compared to those without. We chose to use neurological measures for this purpose, the socalled 'primitive reflexes' (PR). Primitive reflexes are neurological reflexes which are ubiquitously present in the earliest stages of ontogenetic development, in fetal stages and in the newborn and infant (10). They gradually disappear with increasing age, probably as a result of increasing maturation of neocortical areas, notably in the frontal lobe. PR are also found in healthy elderly and are regarded by some as a sign of the physiological aging process (e.g. 20). Evidence exists that PR in mature subjects represent release phenomena, due to a decrease of higher cortical control over lower centres (e.g. 21). When the PR reappear with age, they may be regarded as a subtle measure of changes in brain functioning. It is not clear, however, whether PR which are elicited in presumably healthy subjects are the pure consequence of the physiological aging process itself or that subtle health-related factors such as BLE contribute to the release signs as an age-extrinsic factor.

The prevalence of primitive reflexes has been evaluated by Vreeling, Houx and Jolles in the large cross-sectional study described in earlier paragraphs. An elaborate PR-protocol was made and evaluated in terms of intra-observer and interobserver reliability (10). Nine reflexes were clustered in three groups according to a proposal by Franssen and coworkers (22). Thus, the glabellartap reflex, the palmomental reflex, the pollicomental reflex and the snout reflex were regarded as 'nociceptive reflexes'. The grasp reflex, the suck reflex and the rooting reflex were in the category of 'prehensile reflexes', and the mouth open finger spread reflex and the nuchocephalic reflex were in the rest-category (references in 10). The nociceptive reflexes are regarded as a measure of subtle changes in brain functioning; they are found already in patients with moderate to severe cognitive dysfunctions without dementia (22). Prehensile signs on the other hand are taken to be a manifestation of quite profound brain dysfunction; these signs are -generally- seen in patients with severe dementia or profound brain destruction after brain infarct or brain tumours.

The PR were tested in the 247 healthy subjects mentioned above. It was found that the prevalence of the prehensiles is essentially zero up till far in the serium. The picture for the nociceptive reflexes is totally different. In BLE subjects, the prevalence of the nociceptive PR was 17% in young subjects, and increased to 35% in middle-aged subjects (41-61 years) 60% in old subjects (70-80 years). In BLE-free subjects on the other hand, the prevalence was 12% respectively 15% and 58%. In is interesting in this respect that there is a large difference in young and middle-aged subjects but not in the old group.

The data suggest that the curves for the subjects without BLE may reflect the physiological aging process, i.e. age-intrinsic processes: Slight changes in brain function are evident in one out of every five to six healthy middle-aged subjects already. This is because BLE free subjects show nociceptive reflexes with a prevalence up till 15%. The age-extrinsic factors appear to compromise brain function as manifested by the appearence of nociceptive PR in the fifth and sixth decade already, for the BLE-group. In conclusion, the BLE give rise to an increased number of nociceptive reflexes in otherwise healthy individuals. This is a strong indication that the BLE may be a causal factor in leading to a change in brain functioning and that they may explain a significant part of cognitive changes.

A follow-up study was performed into PR in patients with Age-Related Cognitive Dysfunction. Fifteen subjects suffering from Age-Associated Memory impairment (23) were compared to carefully age-matched healthy controls. The prevalence of nociceptive reflexes was 50% in the AAMI group, which was highly significant when compared to the controls (5%: Vreeling, Houx and Jolles, 1993 submitted). The interesting hypothesis that these AAMI patients might not only be characterized by enhanced number of PR but also by BLE was investigated in another study in a clinical setting. Sixty-one subjects with memory dysfunctions without dementia or any other neurological or internal disorder were compared to matched controls. The prevalence in BLE subjects aged 70 was 5% to 20% to 30% in BLE subjects aged 80. In BLE subjects a prevalence of 0% respectively 5% was found. The patients had an average of 1.6 BLE as compared to 0.4 BLE in the control group. This difference was statistically significant. (Verhey, Houx, Vreeling and Jolles in preparation). These data are of importance because it is now shown that this non-demented group with difficult-to-judge cognitive complaints is characterized by both PR and by BLE. This is evidence in favour of the notion that brain function is compromized in this group more than can be explained by age-intrinsic processes. In other words, some organic and age-extrinsic factor is primarily responsible for cognitive complaints and deficits in this group.

CONCLUDING REMARKS

This paper reviews recent research findings suggesting that age-extrinsic factors -Biological Life Events- may have a stronger influence on cognitive performance in elderly subjects than calender age as such. Healthy subjects who do not complain about cognition, when characterized by BLE, have inferior performance on cognitive tests. On the other hand, when elderly subjects do complain about memory and have a deficient performance on neurocognitive tests (age-related memory impairment), they have much higher chance of having a BLE. Finally, middle-aged subjects with BLE have much higher prevalence of nociceptive reflexes which are regarded as a subtle sign of functional changes in the brain. In addition, memory-disturbed elderly patients have still much higher prevalence of PR. Taken together, the fact that PR are found in subjects especially when they have suffered a BLE or have memory dysfunctions, emphasizes the notion that the BLE and memory dysfunctions may be the cause, respectively the consequence of (subtle) brain dysfunction. Because the health related factors have not been taken into account in the majority of gerontological studies up till now, the findings presented here may present new avenues for investigating the individual differences which are known to occur in the aging process. More information as to the determinants of both successful aging and accelerated or pathological aging is needed. The BLE may prove relevant in this respect. More research is needed to investigate whether BLE are predictors of dementing conditions such as Alzheimer's disease. In addition, primitive reflexes may be a relevant research tool in the investigation of subtle brain changes in subjects in which investigation of structural brain changes with advanced technology is not possible. The present results with respect to PR suggest that they may yield relevant findings in neurogerontological research.

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